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Improved survival of patients with primary distant metastatic breast cancer in the period of 1995 – 2008.

A nationwide population-based study in the Netherlands

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Abstract

Purpose In this study changes in prognosis for more than 8000 patients with primary distant metastatic breast cancer were analyzed, using nation-wide data of the Netherlands Cancer Registry. Besides the roll of systemic treatment, the effect of surgery of the primary tumor was evaluated.

Methods Between 1995 and 2008, 160,595 new patients were diagnosed with invasive breast cancer. Of these patients, 8,031 (5.0%) had distant metastases at diagnosis. Patients were divided into three periods, based on the year of diagnosis of their disease.

Results The median survival was 1.42 years for patients diagnosed in the period 1995-1999, 1.61 years in the period 2000-2004 and 1.95 years in the period 2005-2008. The improvement of the median survival was most pronounced for patients younger than 50 years. Patients receiving systemic treatment, loco-regional radiotherapy or breast surgery had a significantly lower risk of death compared to patients not receiving these treatments.

Conclusions An improvement of 6 months is observed in the median survival of patients with primary distant metastatic breast cancer between 1995 and 2008. The increased efficacy of chemotherapy and the introduction of targeted treatments are the most likely explanations for this improvement, which was most marked for younger patients.

Key words

Breast cancer, metastatic disease, prognosis, surgery, systemic treatment

Introduction

Approximately 3-10% of all patients with breast cancer have distant metastases at initial presentation, and this proportion has decreased only slightly during the last three decades [1,2]. As in general metastatic breast cancer cannot be cured, patients receive palliative treatment. These include hormonal treatment, chemotherapy and targeted therapy. Local treatment of the primary tumor is usually not part of the standard therapy and is only recommended in case of symptomatic local disease.

During the last fifteen years, important changes have taken place concerning systemic treatment for patients with metastasized breast cancer, such as the introduction of taxanes in the late nineties and aromatase inhibitors and targeted therapy like trastuzumab in the beginning of the twenty-first century. A systematic review of trials has demonstrated that increased efficacy of chemotherapy and targeted treatments have resulted in important improvements in the survival of patients with metastatic or recurrent disease [3]. It would be interesting to know whether these improvements have also taken place in the general population among the patients with primary distant metastatic breast cancer, treated in routine clinical practice outside clinical trials.

In a previous study we reported an increased survival in the Netherlands of patients with primary metastatic breast cancer. In this study, which was based on 1,089 patients diagnosed in South-East Netherlands in the period 1975-2002, the median survival remained unchanged between 1975 and 1984, but increased

from 17 months for the patients diagnosed in the period 1985-1994 to 20.5 months for those diagnosed in the period 1995-2002 [4].

In the current study, we analyzed the changes in prognosis for more than 8,000 patients with primary distant metastatic breast cancer diagnosed between 1995 and 2008 and followed until 2010, using nation-wide data of the Netherlands Cancer Registry. As described above, surgery of the primary tumor is not standard treatment in these patients, though several retrospective studies have shown an improvement in overall survival in patients who have received breast surgery [5-11]. Therefore, we also analyzed the impact of surgical resection of the primary breast tumor, besides the role of systemic treatment.

Patients and methods

Patients

Patients were selected from the population based Netherlands Cancer Registry. PALGA, the nationwide Dutch network and registry of histo- and cytopathology, regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Following this notification, trained registry personnel from the Netherlands Cancer Registry collect data on patient and tumor characteristics, diagnosis, staging and treatment. Coding of the items is based on the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers.

According to the database the Netherlands Cancer Registry, 160,595 new patients were diagnosed with invasive breast cancer in the period 1995-2008. Of these patients, 8,031 (5.0%) had distant metastases at diagnosis (stage IV disease).

To establish whether improvement of prognosis had taken place, patients were divided into three periods, based on the year of diagnosis of their disease; 1995-1999, 2000-2004 and 2005-2008. The follow-up of these patients was completed until January 1, 2010. Information about the age of the patients at time of diagnosis and tumor size of the primary tumor was recorded. Clinical tumor size was used for patients who did not undergo surgery. Also, information was collected about the type of treatment received by the patients, including systemic treatment, loco-regional radiotherapy and surgery of the primary tumor. No details on the extent and completeness of the surgical procedure were available. Only the first line of systemic therapy was documented by the Netherlands Cancer Registry and information on the type of systemic treatment was only available for the type of treatment (hormone treatment, chemotherapy, targeted treatment), but not for the exact drugs used. Use of targeted treatment has only been documented since 2005.

Statistical analyses

Survival time was defined as the period between the date of diagnosis and the date of death or January 2010 for the patients who were still alive. Overall survival rates were calculated using the Kaplan-Meier method. The log-rank test

was performed to evaluate significant differences between survival curves in univariate analyses. Multivariable analyses were carried out using Cox proportional hazards regression models. The variables inserted into the model were period of diagnosis (2000-2004 and 2005-2008 versus 1995-1999), age at diagnosis (50-69 and 70+ versus <50 years), tumor size (T3-4 versus T1-2), surgery of the primary tumor (yes versus no), loco-regional radiotherapy of the primary tumor (yes versus no) and the use of systemic treatment (yes versus no). Hazard ratios (HR) with 95% confidence intervals (CI) and P-values were estimated with respect to the reference category for each covariate. The SAS computer package (version 9.2) was used for all statistical analysis (SAS Institute Inc., Cary, NC, USA, 1999).

Results

Patient characteristics

The proportion of patients with primary metastatic breast cancer (stage IV disease) decreased from 5.3% (2,688/51,226) in the period 1995-1999, to 5.0% (2,916/58,679) in the period 2000-2004 and to 4.8% (2,427/50,690) in the period 2005-2008 (P=.003). The proportion of patients with a breast tumor of five centimeter or smaller (T1 and T2 classification) increased from 47% in the period 1995-1999 to 55% in the period 2005-2008 (Table 1). More than 20% of all patients with stage IV breast cancer were younger than 50 years, 37% were between 50 and 70 years and 42% were 70 years or older (Table 1). The

proportion of patients in the age group of 50-69 year was somewhat higher in the period 2005-2008.

The proportion of patients receiving first-line systemic therapy remained rather stable during the three periods (Table 1). Loco-regional radiotherapy as first-line treatment was administered to 14% of all patients in the period 1995-1999, to 15% in the period 2000-2004 and to 11% in the period 2005-2008 (Table 1). The proportion of patients who underwent a resection of the breast tumor (either ablation of the breast or lumpectomy, with or without axillary lymph node dissection) decreased from 31% in the period 1995-1999 to 23% in the last period (Table 1).

Older patients were less likely to receive chemotherapy and targeted treatment and more likely to receive hormonal treatment as first-line treatment (Table 2). In the period 2005-2008, 20% of the patients <50 years received a targeted treatment, compared to 11% of the patients of 50-69 years and 3% of those of 70 years or older (P<.0001). Older patients were also less likely to undergo surgery and to receive loco-regional radiotherapy (Table 2). In the period 2005-2008, 38% of the patients <50 years underwent surgery, compared to 24% of the patients of 50-69 years and 15% of those of 70 years or older (P<.0001).

Median survival

The median survival was 1.42 years for patients diagnosed in the period 1995-1999, 1.61 years in the period 2000-2004 and 1.95 years in the period 2005-

2008 (Table 3 and Figure 1). The difference between the periods 1995-1999 and 2000-2004 and between the periods 2000-2004 and 2005-2008 were both statistically significant (P=.012 and P<.0001, respectively). When analyzed according to age group, the improvement of the median survival was most pronounced for patients of 50 years or younger between the periods 2000-2004 and 2005-2008 (Figure 2a and Table 3), with an increase of 2.44 to 3.60 years (P<.0001) and for patients aged 50-69 years between the periods 1995-1999 and 2000-2004 (Figure 2b and Table 3), with an increase from 1.34 to 1.83 years (P=.009). The median survival in patients of 70 years and older did not differ significantly between the three periods (Figure 2c and Table 3). In the first period the median survival was 1.10 years, in the second 1.07 years and in the last period 1.25 years.

Multivariable analysis

In the multivariable analysis, taking into account the age of the patients, the size of the primary tumor and the use of systemic treatment, surgery and radiotherapy, the HR's for mortality in the second and third period as compared to the first period were 0.95 (P=.08) and 0.83 (P<.0001), respectively (Table 4). Older age and larger primary tumor size were associated with a higher mortality risk. Patients receiving systemic treatment (HR 0.34, 95% CI 0.32-0.37), loco-regional radiotherapy (HR 0.79, 95% CI 0.73-0.86) or breast surgery (HR 0.64, 95% CI 0.60-0.68) had a significantly lower risk of death compared to the patients not receiving these treatments. The median survival of the patients

undergoing surgery was 2.56 years, compared to 1.33 years for the patients without surgical treatment of the primary tumor (Figure 3).

A multivariable analysis according to age group, confirmed the increased prognosis of the patients treated in the period 2005-2008 (Table 5). The HR's for the patients treated in this period, as compared to those treated in the period 1994-1999 were 0.66 (95% CI 0.55-0.79) for patients younger than 50 years, 0.81 (95% CI 0.72-0.91) for those of 50-69 years old and 0.85 (95% CI 0.77-0.95) for patient of 70 years or older. In all age groups, the patients receiving systemic treatment, loco-regional radiotherapy or breast surgery had a significantly lower risk of death compared to the patients not receiving these treatments.

Discussion

According to the data of the Netherlands Cancer Registry, the median survival of patients with primary distant metastatic breast cancer has improved with 6 months in the period 1995-2008, now reaching almost 2 years. The improvement was most pronounced in the period 2000-2004 for patients aged 50-69 years and in the period 2005-2008 for the patients younger than 50 years. These improvements were also confirmed by the results of the multivariable analysis, adjusting for potential confounders.

Our nationwide study is one of the few large population-based studies on trends in prognosis of patients with primary metastatic breast cancer. Two other

population-based studies analyzed data from the Surveillance, Epidemiology, and End Results (SEER) program [12,9]. The study by Dawood et al., involving 15,438 patients, showed an improvement of the median survival of 4 months between 1988 and 2003 [12]. In both studies, the increased prognosis of patients treated more recently was confirmed in a multivariable analysis. In a population-based study by Rapiti et al., based on 300 patients diagnosed between 1977 and 1996 and documented by the Geneva Cancer Registry, an improvement of the breast cancer-specific survival was demonstrated in the unadjusted but not in the adjusted multivariable analysis [7]. In a previous population-based study, involving 1,089 patients treated in the southern part of the Netherlands, we observed an improvement of the median survival of 2.5 months for the patients treated in the period 1995-2002 as compared to those treated in the period 1975-1984 [4].

Most studies on trends in prognosis of patients with primary metastatic breast cancer are hospital-based [13], or also included patients with secondary metastatic disease or patients participating in randomized clinical trials comparing different lines of chemotherapy [14-17]. The interval between the primary tumor and the diagnosis of metastatic disease is an important prognostic factor. Therefore, including patients with secondary metastatic disease might introduce bias when differences in the metastasis-free interval exist between patients treated in different time-periods. Inclusion of patients treated in trials could also lead to biased results as they tend to have a better prognosis than patients receiving the same treatment outside trials, probably because of the

strict in- and exclusion criteria applied to trial populations [18,19]. Similar to our study, a hospital-based study by Andre et al., including 724 patients, also showed an improvement in the median survival of 6 months; being diagnosed between 1994 and 2000 was associated with a 37% lower risk of mortality in comparison to patients diagnosed between 1987 to 1993 [13]. None of the studies described above covered a patient group treated after 2003. Our study, which contains data of patients treated until 2009, is the first to evaluate the possible impact in daily practice of the treatments that have been introduced mainly since that time, such as trastuzumab.

Patients with primary metastatic disease are thought to have more aggressive disease than patients with metastases diagnosed during follow-up after treatment of primary breast cancer, and therefore their prognosis might be poorer. On the other hand, use of chemotherapy and endocrine treatment in the adjuvant setting may induce drug resistance and leave fewer options for optimal systemic treatment when metastases occur. A large population-based study from Canada by Chia et al. on 2,150 patients with metastatic breast cancer, of whom only 21% had primary metastatic disease, showed that the median survival improved from 1.2 years for patients diagnosed in the period 1991-1992 to 1.6 years for those diagnosed in the period 1999-2001 [15]. These figures suggest that there is not a large difference in the survival between patients with primary and secondary metastatic breast cancer.

The proportion of patients with stage IV breast cancer receiving first-line systemic treatment did not change during the study period. Therefore, the

introduction of more effective drugs is the most likely explanation for the better prognosis of patients treated after 1999. The fact that the benefit was larger for patients younger than 50 years is supported by the more frequent use of targeted treatment among this age group in the period of 2005-2008, when 20% received targeted therapy as first-line treatment, compared to 11% of the patients between 50 and 70 years old and only 3% of those older than 70 years.

Patients of 70 years and older had a poor prognosis, which improved only slightly during the study period. This may be explained by the fact that chemotherapy and targeted treatment were less frequently used in the elderly. Elderly patients were also less likely to undergo surgery or receive loco-regional radiotherapy. Other studies, with respect to the prognosis of elderly patients, show a significantly higher mortality risk in older patients with metastatic disease [7,9,11]. Comorbidity and frailty are more common among older patients and limit the therapeutic choices [20]. This may be an important explanation for the fact that the prognosis in elderly women with metastatic breast cancer has improved much less than in women younger than 70 years.

In our study, surgical treatment of the primary tumor was associated with lower mortality in all age groups. During the study period, the proportion of patients treated with surgery decreased. In a previously published review of the literature we found a pooled hazard ratio of 0.65 (95% CI, 0.59-0.72) in favor of surgical treatment of the breast tumor [21], which is almost equal to the HR calculated in the current study. One of the explanations for the effect of surgery is that removing the tumor will lower the tumor load and reduce the amount of

circulating tumor cells in the blood, which is known to be an independent predictor of overall survival in patients with metastatic breast cancer [22]. Nevertheless, the observational nature of our study does not allow us to draw strong conclusions about the causality of the association between surgery and survival. Loco-regional radiotherapy also appeared to be associated with a significant improvement of the median survival. A similar association was found in a study by Le Scodan et al., in which radiotherapy was an independent prognostic factor in multivariate analysis, with a hazard ratio of 0.70 (95% CI, 0.58 to 0.85) [23].

Our population-based study is based on information from more than 8,000 patients with primary distant metastatic breast cancer, gathered by the Netherlands Cancer Registry and including virtually all patients with stage IV breast cancer in the Netherlands. Information of patients diagnosed until 2009 was available, with follow-up until 2010, which allowed us to provide up-to-date results. Unfortunately, only first-line treatment was recorded and no data were available on the specific drugs used. This is clearly a limitation of a retrospective analysis based on cancer registry data. This may also explain why the sum of first-line hormonal therapy and chemotherapy is larger than 100%, that is, for some patients more than one treatment modality may have been recorded, perhaps in those who had an early switch because of non-responsiveness to the first initiated treatment. Obviously, also other biases may have occurred, for instance by patient selection for specific therapies like radiotherapy or surgery.

Twelve percent of the patients in our study did not receive systemic treatment. Some underreporting cannot be ruled out. However, in two other studies on prognosis of primary metastatic breast cancer by Blanchard et al. and Kahn et al. similar percentages, of 8% and 22% respectively, were reported [5, 10]. Apparently, a substantial part of these patients present with very advanced, rapidly progressive disease for which systemic treatment is no viable option anymore.

Information on the use of targeted treatment was only available since 2005, as was also the case for the site of distant metastatic involvement. However, it is not very likely that these sites and the number of metastatic sites have changed much during the three time periods. Our study is covering a relatively short period, which makes it less likely that changes in radiologic facilities (except perhaps for the introduction of positron emission tomography) have had a large impact on the detection of metastatic disease. Moreover, the percentage of patients with metastatic disease has remained rather stable during the different time periods, also indicating that screening methods and indications for peri-operative screening for patients without clinical signs of metastases have not changed between 1995 and 2008. An increase in the amount of patients participating in the breast cancer screening program may have caused the increase in the proportion of patients with T1 and T2 tumors. However, in the multivariable analysis adjustments have been made for this shift in tumor size.

In conclusion, an overall improvement of 6 months is observed between 1995 and 2008 in the median survival of patients with primary distant metastatic

breast cancer, resulting in a median survival of almost 2 years for the patients treated in the last period. This improvement was most pronounced in patients younger than 50 years. The increased efficacy of chemotherapy and the introduction of targeted treatments are the most likely explanation. Surgical removal of the primary breast tumor and loco-regional radiotherapy do also seem to have a positive impact on survival, but to be able to rule out selection bias, it would require a randomized study to quantify the added value of loco-regional treatment and tumor control to systemic therapy in the management of patients with stage IV breast cancer.

Conflict of interest

The authors indicated no potential conflicts of interest.

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Table 1: Characteristics of patients with primary metastatic breast cancer, according to period of diagnosis (N=8031)

Characteristic	*Period of diagnosis*						
	1995-1999 (N=2688)		*2000-2004 (N=2916)*		*2005-2008 (N=2427)*		
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*P*
Age at diagnosis (year)							.003
<50	543	(20)	642	(22)	519	(21)	
50-69	961	(36)	1065	(37)	965	(40)	
70+	1182	(44)	1209	(41)	943	(39)	
Tumor size							<.0001
T1-2	1098	(47)	1275	(50)	1198	(55)	
T3-4	1233	(53)	1286	(50)	992	(45)	
Missing	357		299		237		
Surgery							<.0001
Yes	831	(31)	810	(28)	563	(23)	
No	1857	(69)	2106	(72)	1864	(77)	
Radiotherapy							.002
Yes	367	(14)	428	(15)	278	(11)	
No	2321	(86)	2488	(85)	2149	(89)	
Systemic treatment							.001
Yes	2404	(89)	2514	(86)	2142	(88)	
No	284	(11)	402	(14)	285	(12)	

Table 1: Characteristics of patients with primary metastatic breast cancer, according to period of diagnosis (N=8031). (Continued)

Characteristic	*Period of diagnosis*						
	1995-1999 (N=2688)		*2000-2004 (N=2916)*		*2005-2008 (N=2427)*		
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*P*
Chemotherapy							.001
Yes	883	(33)	1086	(37)	906	(37)	
No	1805	(67)	1830	(63)	1527	(63)	
Hormonal treatment							.001
Yes	1763	(66)	1781	(61)	1571	(65)	
No	925	(34)	1135	(39)	856	(35)	
Targeted treatment	Not available		Not available				Not applicable
Yes					245	(10)	
No					2182	(90)	

Table 2: Treatment characteristics of patients with primary metastatic breast cancer, according to age group (N=8031)

Characteristic	*Age at diagnosis (years)*						
	<50 (N=1706)		*50-69 (N=2991)*		*70+ (N=3334)*		
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*P*
Surgery							<.0001
Yes	676	(40)	875	(29)	653	(20)	
No	1030	(60)	2116	(71)	2681	(80)	
Radiotherapy							<.0001
Yes	315	(18)	453	(15)	305	(9)	
No	1391	(82)	2238	(85)	3029	(91)	
Systemic treatment							<.0001
Yes	1604	(94)	2660	(89)	2796	(84)	
No	102	(6)	331	(11)	538	(16)	
Chemotherapy							<.0001
Yes	1169	(69)	1336	(45)	370	(11)	
No	537	(31)	1655	(55)	2964	(89)	
Hormonal treatment							<.0001
Yes	819	(48)	1746	(58)	2550	(76)	
No	887	(52)	1245	(42)	784	(24)	
Targeted treatment*							<.0001
Yes	104	(20)	109	(11)	32	(3)	
No	415	(80)	856	(89)	911	(97)	

* Only available for patients diagnosed in the period 2005-2008

Table 3: Median survival (yrs) and 95% confidence intervals of patients with primary metastatic breast cancer, according to age group and period of diagnosis

Age group	*Period of diagnosis*			
	1995-1999	*2000-2004*	*2005-2008*	*P*
<50 yrs	2.29 (2.09-2.74)	2.44 (2.12-2.78)	3.60 (2.88-4.14)	<.0001
50-69 yrs	1.34 (1.20-1.51)	1.83 (1.64-2.03)	2.07 (1.90-2.40)	<.0001
70+ yrs	1.10 (0.92-1.25)	1.07 (0.92-1.18)	1.25 (1.08-1.38)	.200
All patients	1.42 (1.33-1.53)	1.61 (1.51-1.70)	1.95 (1.80-2.08)	<.0001

Table 4: Multivariable analysis for time until death for patients with primary metastatic breast cancer (N=7073)*

Characteristic	*HR***	*(95% CI)*	*P*
Period of diagnosis			
1995-1999	1 (Ref)		
2000-2003	0.95	(0.89-1.01)	.081
2004-2007	0.83	(0.77-0.89)	<.0001
Age at diagnosis (years)			
<50	1 (Ref)		
50-69	1.33	(1.24-1.44)	<.0001
70+	1.59	(1.48-1.71)	<.0001
Tumor size			
T1-2	1 (Ref)		
T3-4	1.14	(1.08-1.20)	<.0001
Surgery			
No	1 (Ref)		
Yes	0.64	(0.60-0.68)	<.0001
Systemic treatment			
No	1 (Ref)		
Yes	0.34	(0.32-0.37)	<.0001
Radiotherapy			
No	1 (Ref)		
Yes	0.79	(0.73-0.86)	<.0001

* 958 patients were not included in the multivariable because of missing information on tumor size
** HR = Hazard Ratio

Table 5: Multivariable analysis for time until death for patients with primary metastatic breast cancer, according to age group

Characteristic	Age group								
	<50 (N=1529)			*50-69 (N=2586)*			*70+ (N=2958)*		
	HR	*(95% CI)*	*P*	*HR*	*(95% CI)*	*P*	*HR*	*(95% CI)*	*P*
Age, per year increase	0.99	(0.98-1.00)	.030	1.01	(1.00-1.02)	.006	1.02	(1.01-1.03)	<.0001
Period of diagnosis									
1994-1999	1 (Ref)			1 (Ref)			1 (Ref)		
2000-2003	0.98	(0.86-1.12)	.722	0.92	(0.83-1.02)	.110	0.94	(0.86-1.02)	.140
2004-2007	0.66	(0.55-0.79)	<.0001	0.81	(0.72-0.91)	.0004	0.85	(0.77-0.95)	.002
Tumor size									
T1-2	1 (Ref)			1 (Ref)			1 (Ref)		
T3-4	1.33	(1.17-1.50)	<.0001	1.18	(1.08-1.29)	.0003	1.05	(0.97-1.13)	.237
Surgery									
No	1 (Ref)			1 (Ref)			1 (Ref)		
Yes	0.69	(0.61-0.79)	<.0001	0.64	(0.58-0.71)	<.0001	0.64	(0.58-0.70)	<.0001
Systemic treatment									
No	1 (Ref)			1 (Ref)			1 (Ref)		
Yes	0.43	(0.34-0.54)	<.0001	0.40	(0.35-0.46)	<.0001	0.31	(0.28-0.35)	<.0001
Radiotherapy									
No	1 (Ref)			1 (Ref)			1 (Ref)		
Yes	0.72	(0.61-0.85)	<.0001	0.79	(0.70-0.89)	<.0001	0.85	(0.75-0.97)	.019

Legends to figures

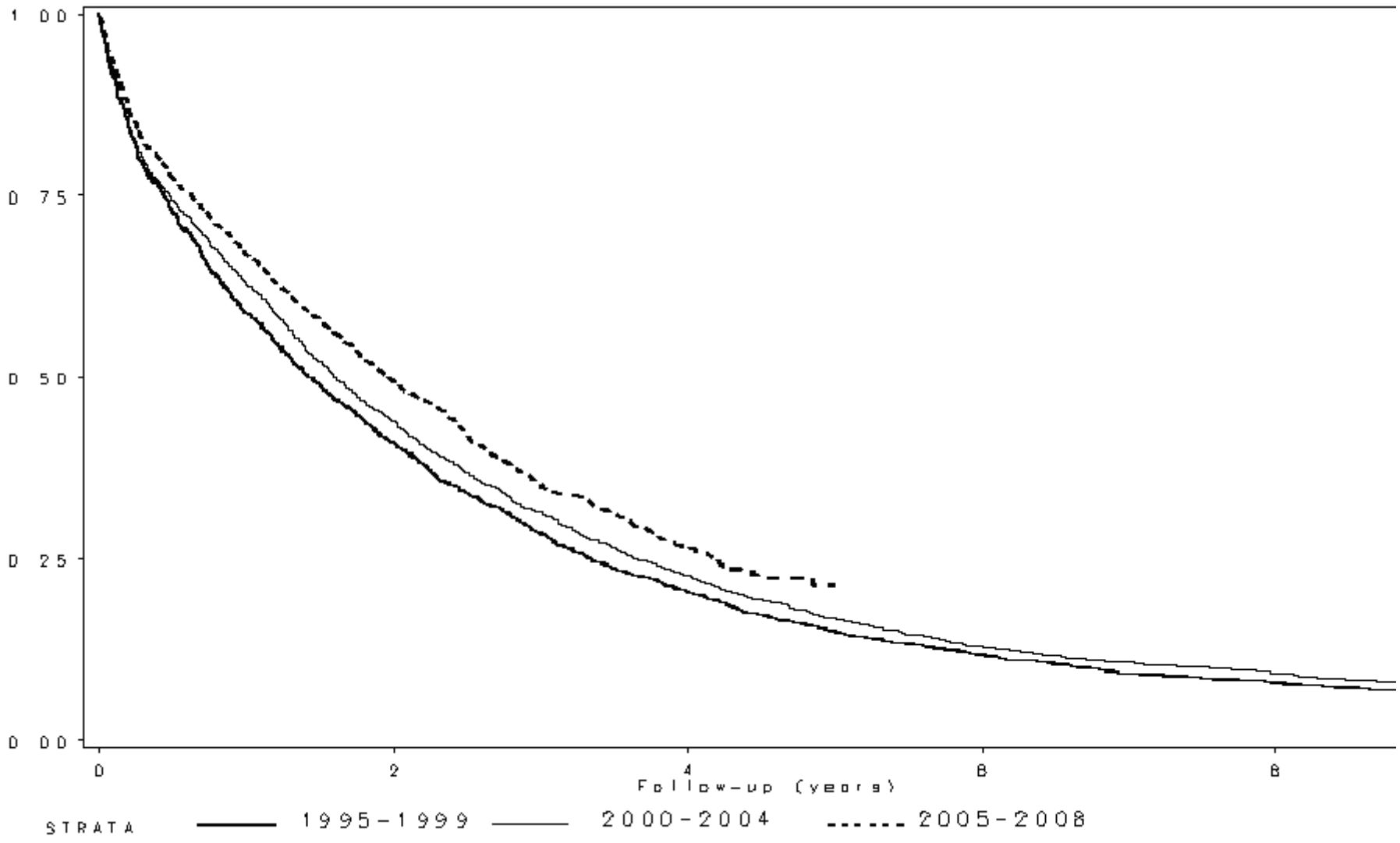
1. Overall survival of patients with primary metastatic breast cancer according to period of diagnosis.

2a. Overall survival of patients with primary metastatic breast cancer aged younger than 50 years, according to period of diagnosis.

2b. Overall survival of patients with primary metastatic breast cancer aged 50 to 69 years, according to period of diagnosis.

2c. Overall survival of patients with primary metastatic breast cancer aged 70 years or older, according to period of diagnosis.

3. Overall survival of patients with primary distant metastatic breast cancer, according to surgical removal of the primary tumor.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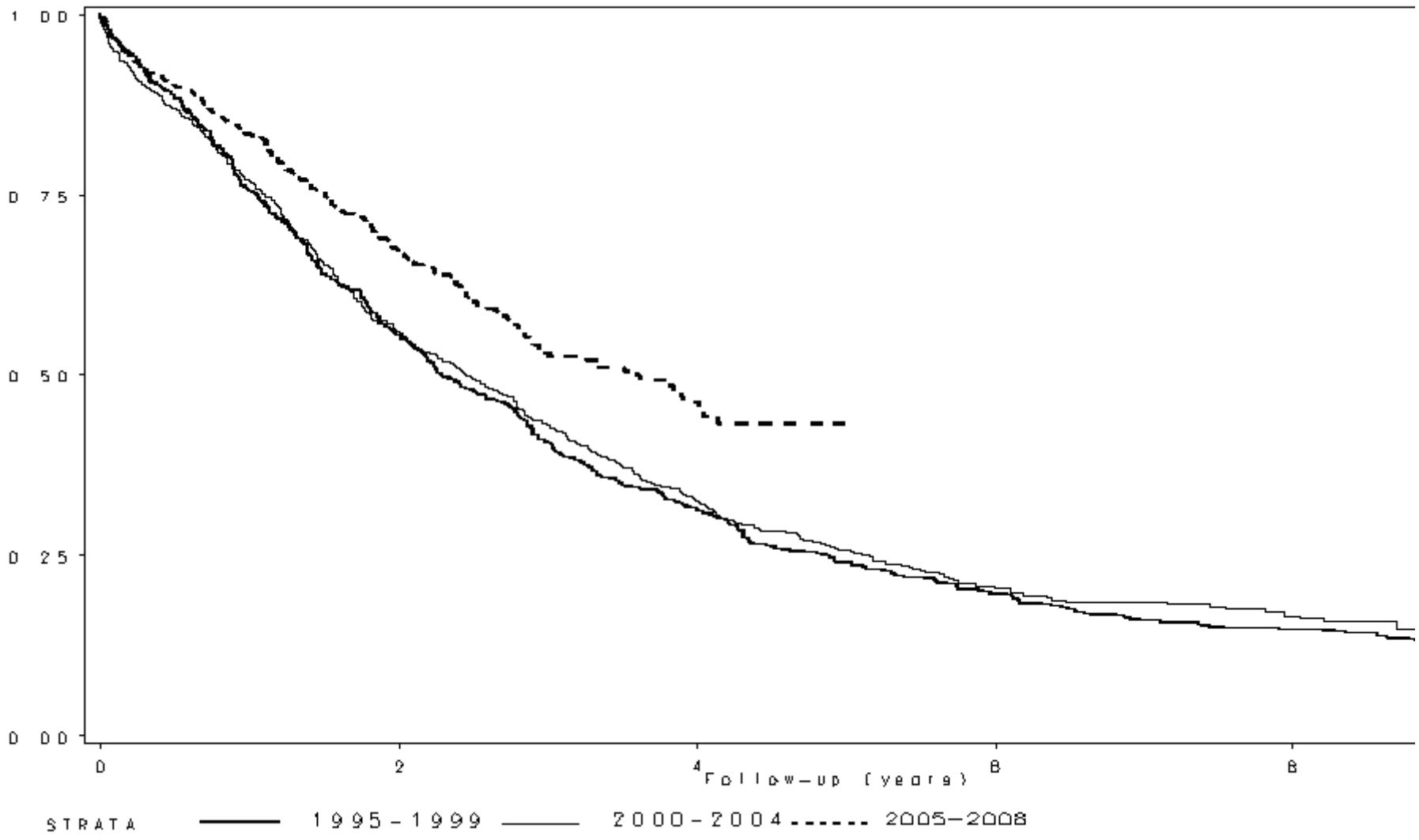
0 25
0 00
0
2
4
6
8
Follow-up (years)
STRATA
1995-1999
2000-2004
2005-2008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0 75
0 50
0 25
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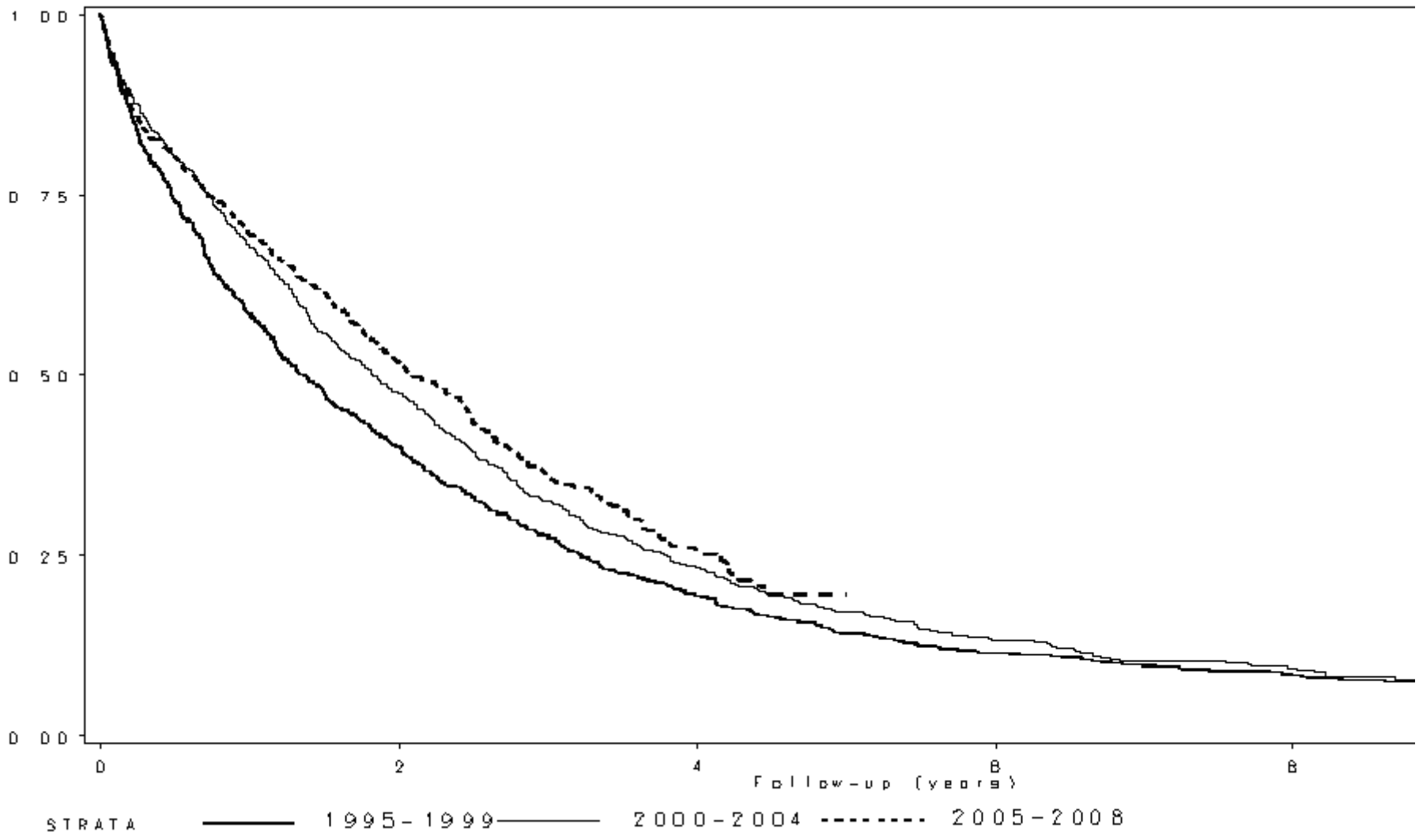
2
4
6
8
Follow-up (years)
STRATA
1995-1999
2000-2004
2005-2008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0 50
0 25
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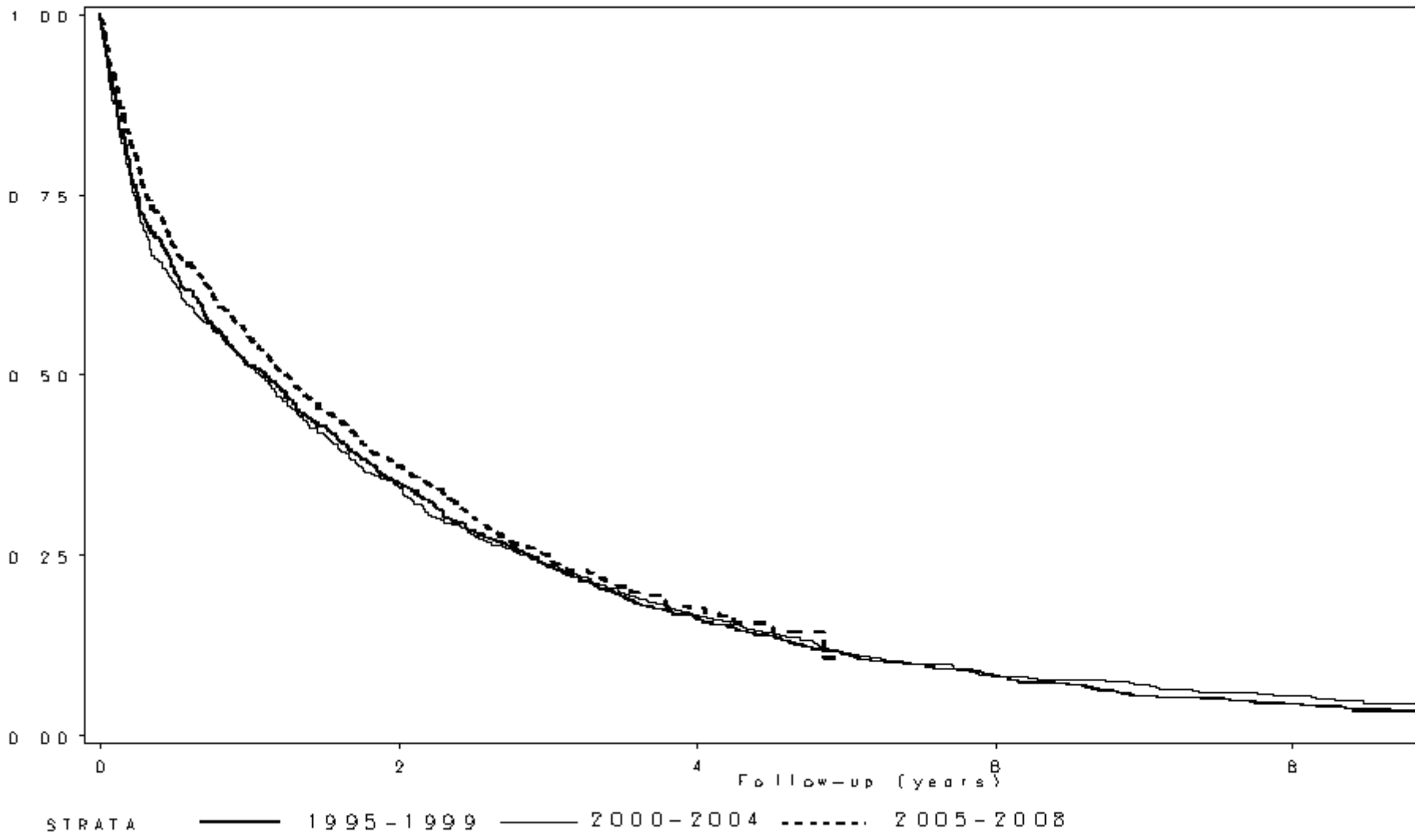
0
2
4
6
8
Follow-up (years)
STRATA
1995-1999
2000-2004
2005-2008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0 75
0 50
0 25
0 00
0
2
4
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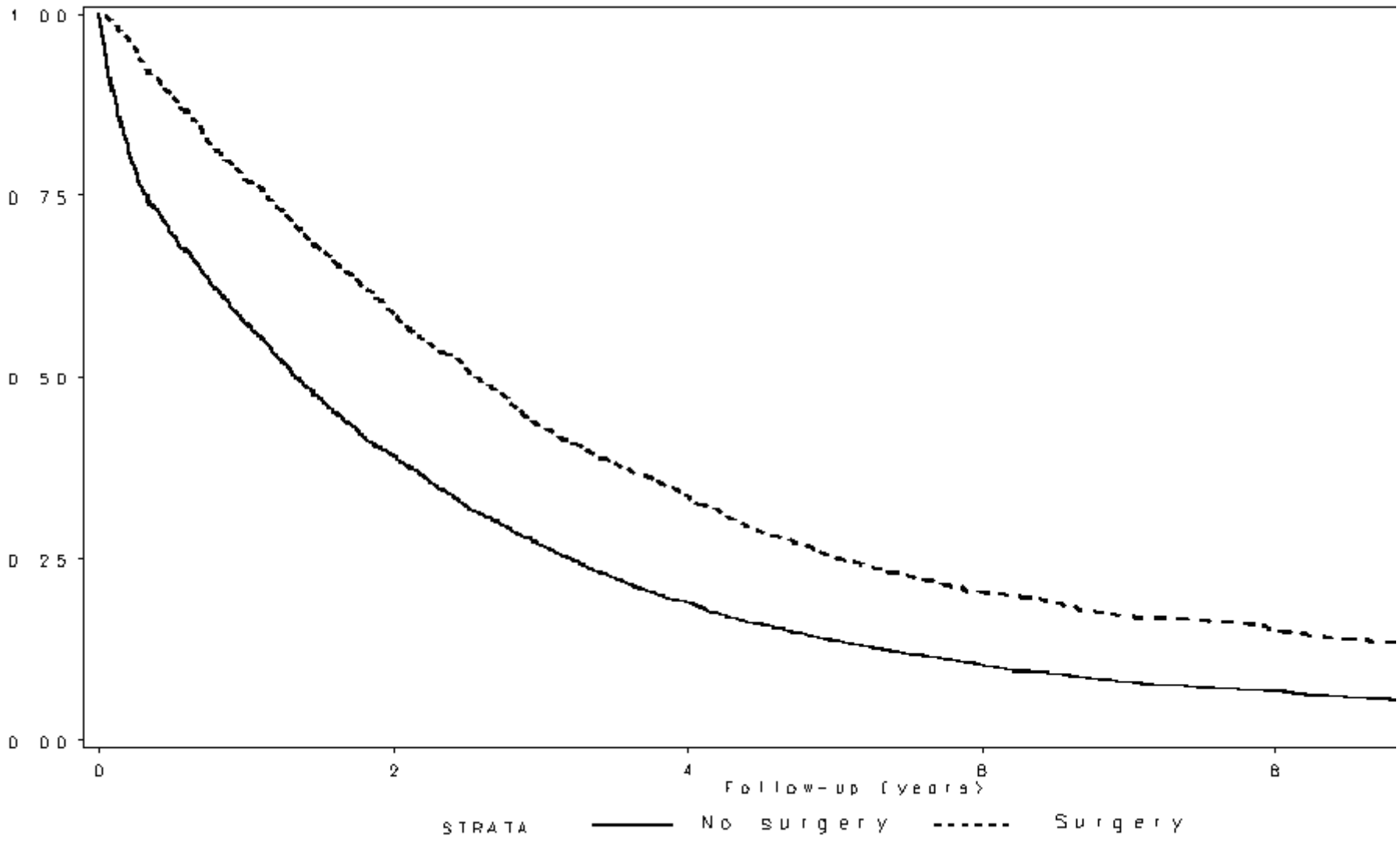
8
Follow-up (years)
STRATA
1995-1999
2000-2004
2005-2008


1 00
0 75
0 50
0 25
0 00
0
2
4
6
8
Follow-up (years)
STRATA
No surgery
Surgery